

## REMARKS

The last Office Action of June 1, 2004 has been carefully considered. Reconsideration of the instant application in view of the foregoing amendments and the following remarks is respectfully requested.

Claims 20-26, 28-36 and 38-49 are pending in the application. Claims 27 and 37 have been, previously, canceled. Claims 20-23, 26, 28-36, 38, and 44-48 have been amended in response to the comments by the Examiner and in an effort to overcome the rejections made under 35 USC § 112, second paragraph. A total of 28 claims is now on file. No claim surcharge is due. An amendment to the specification on page 6 has been made.

Applicants have amended the specification in an effort to correct a typographical error in the structural formula appearing at page 6 as well as in claim 31. Support for the amendments to both the claims and specification are found in the original claims as well as the specification as a whole.

It is noted that claims 20-26, 28-36, and 44-49 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Pending claims 20-26, 28-36, and 38-49 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 20-25 and 44-47 stand rejected under 35 U.S.C. §103(a) as being unpatentable over each of the references as cited from PTO form 1449. Hallas (reference Y of PTO 1449) (hereinafter: "Hallas"), Aaron et. Al. (reference X of PTO 1449) (hereinafter: "Aaron"), Aaron et. al [R] (J. Chem. Soc. (1963) pp 2655-2662) (hereinafter: "Aaron II"), Barker et al (J. Chem. Soc. section B: Physical Organic} (1969), vol. 9 pp 1068-1071 (hereinafter: "Barker") or U.S. Patent No. 4,320,940 (hereinafter: "Mueller") taken in combination with each of U.S. Patent No. 5,561,045 ("Dorval") or U.S. Patent No. 6,183,968 ("Bandman").

Applicants submit that all of the rejections are addressed by the newly submitted amendments to the claims and the remarks which follow. Accordingly, applicants respectfully request entry of these amendments as rendering the claims allowable or at the very least significantly reduces the issues on appeal. For ease of consideration by the Examiner, applicants have referred to the paragraph numbers used by the Examiner in the Office Action of June 1, 2004. Reconsideration of the instant application in view of the foregoing amendments and the following discussion is respectfully requested.

#### **REJECTION OF CLAIMS 20-37 UNDER 35 U.S.C. §112, FIRST PARAGRAPH**

At pages 5 and 6, paragraph 6 of the Official Action of June 1, 2004 (OA), the Examiner has rejected claims 20-36 and 44-49 under 35 USC § 112, first paragraph stating:

The specification, while being enabling for the preparation of some of the compounds of formula I of claim 20 which contain the groups

$-N(R_{11})(R_{12})$  and  $=N^+(R_9)(R_{10})$  as described in claim 38, does not reasonably provide enablement for the preparation of compounds of formula I wherein either or both of  $-N(R_{11})(R_{12})$  and  $=N^+(R_9)(R_{10})$  are replaced by the groups  $-OR_9$  and/or  $=O$ .

Initially, applicants note that the examples presented in the specification are exemplary of the possible processes and are not intended to be read as limiting the methodology of preparing the compounds or related compounds in any way. Further, applicants urge the Examiner to consider the process described at page 28 of the specification which describes the further processing of the compound designated JF 17 (Note structural formula at page 13 of the Specification) which is heated to reflux for 1 hour in 30 ml of a solution of 3g of sodium hydroxide in ethanol/water, cooled and neutralized. The product is isolated. The process, thus, describes the preparation of Compound JF42 (Note structural formula at page 15 of the specification) wherein the  $-N(R_{11})(R_{12})$  and  $=N^+(R_9)(R_{10})$  groups have been replaced with  $=O$  and  $-O-$   $[-OR]$ , respectively. This process reasonably appears to be equally applicable to the other compounds produced as described in the specification wherein those compounds containing  $-N(R_{11})(R_{12})$  and  $=N^+(R_9)(R_{10})$  maybe subsequently treated to replace either or both of these groups with the corresponding "O" derivative. At the very least, this example should be regarded as providing sufficient guidance to those skilled in this art as to enable those skilled in the art to practice the invention as required by 35 USC § 112, first paragraph.

For the forgoing reasons, withdrawal of the rejection of claims 20-26, 28-36 and 44-49 under 35 USC § 112, first paragraph is respectfully requested.

**REJECTION OF CLAIMS 20-26, 28-36, AND 38-49 UNDER 35 U.S.C. §112,  
SECOND PARAGRAPH**

The Examiner has rejected claims 20-25 and 44-47 under 35 USC § 112, second paragraph as being incomplete for omitting essential steps. (OA, page 2). Applicants have modified claim 20, in accordance with the Examiner's suggestion, to make use of Jepson terminology. Since applicants' invention resides in the use of the disclosed novel dyes as labeling agents in appropriate assays, this language is consistent with applicants' intent and understanding of their invention. Thus, applicants respectfully request that the Examiner reconsider this ground of rejection and that she withdraws the rejection of claims 20-25 and 44-47 on this basis.

In addition, the Examiner has rejected claims 20-26, 28-36, and 38-49 under 35 USC § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. (OA, pages 2-5). The current amendments to the claims and the remarks which follow address each of the issues raised by the Examiner in turn. Applicants note that the amendments to the claims which accompany this response are intended to clarify all of the claims in a manner which is consistent with the requirements of 35 USC § 112, second paragraph as well as overcome the basis for this rejection.

With respect to paragraph 5 a) of OA - Claim 20 has been modified to clarify the definition of variables  $R_9$ - $R_{12}$ . The amended language clarifies the

nature of substituents and which are intended by each definition. Further, the proviso which reads:

with the proviso that if R<sub>1</sub>-R<sub>3</sub> and R<sub>5</sub>-R<sub>7</sub> are hydrogen and R<sub>8</sub>, R<sub>8a</sub> and R<sub>9</sub>-R<sub>12</sub> are methyl, then R<sub>4</sub> is not one of hydrogen, hydroxyl, methyl, isopropyl, t-butyl, phenyl, o-tolyl, p-tolyl, 2,6-dimethylphenyl, 2-t-butylphenyl, 2-isopropenylphenyl and 4-dimethylaminophenyl

has been added to claim 20 to further distinguish the claimed subject matter from the prior art as will be discussed later.

With respect to paragraph 5 b) – Claim 20 has been modified so as to clarify which variables or “R” groups participate in the bridging to form rings. While the Examiner has suggested that the claims be limited to those specific compounds appearing at pages 6 through 16 of the specification, this may unduly limit the scope of the claimed subject matter and applicants regard the presently claimed subject matter as appropriate given the nature of the invention and the disclosure presented in support thereof.

With respect to paragraph 5 c) – The phrase “at least one of “has been removed from all claims, where appropriate, and replaced with Markush language or alternative selection.

With respect to paragraph 5 d) – Claim 20 has been modified by changing the term “hydrocarbon” to alkyl and by making polyethers, and other groups stand alone as individual possibilities for the corresponding R groups. In order to overcome what the Examiner considers confusing concerning the use of the term “hydrocarbon” to indicate compounds or substituents which included hydrogen and carbon, but might additionally include other atoms is easily avoided, it is

believed that the present language is clear as to the nature of each of the possible R groups.

With respect to paragraph 5 e) - Claim 20 has been amended to clarify the situation where either or both of the groups  $-N(R_{11})(R_{12})$  and  $=N^+(R_9)(R_{10})$  can be replaced with either  $-OR_9$  or  $=O$ .

With respect to paragraph 5 f) – Both claims 20 and 26 have been modified in an attempt to clarify for the Examiner the relationship between the R groups when they are involved in a bridging to form one or more ring systems. By referencing the individual R groups and requiring that they be adjacent to each other to form a ring system, the confusing about the bridging groups is eliminated.

With respect to paragraph 5 g) – Claim 20 has been modified to provide antecedent basis for “aromatic ring system” in claim 26, on which it depends and thus for claim 29 which depends on claim 26.

With respect to paragraph 5 h) - The Examiner has raised an issue of antecedent support for compounds IVC, IVD and IVE of claim 31. Both claim 31 and page 6 of the Specification have been modified to correct the typographical error caused by reversal of the groups designated as the  $R_{11}$  and  $R_{12}$  substituent. Applicants note however, that prior to formation of a ring system the nitrogen is singly bonded to the ring to which it is attached. Thus, the nitrogen and substituents thereon are free to move around that single bond to any orientation. However, for consistency and to maintain clarity in both the claims and the specification, these structures have been modified. Applicants further note that

the remainder of the specification provides support for the modifications to the structures in question.

With respect to paragraph 5 i) - Claims 32 -36 has been modified to overcome this rejection. The nature and purpose of the coupling group is now clarified in that it serves to bind or connect the label to the biomolecule being used in the assay. The examples of specific coupling molecules are identified in claim 33. Claim 34 is directed to those compounds where the label of this invention is bound either to a carrier or a biomolecule or in the situation of a "sandwich assay" to both a carrier and a biomolecule. Claim 35 is directed to the invention and provides a list of possible carriers to which the label may be bound. Claim 36 is directed to those situations where the label of the invention is bound, via a coupling moiety to a biomolecule selected from a defined group. The nature of these coupling groups are well known and their use, particularly in bioassays such as immunoassays and nucleic acid hybridization assays are so established that one skilled in this art would readily appreciate the nature and purpose of such a coupling agent.

With respect to paragraph 5 j) - Claim 26 has been modified to indicate that the group in question is a 4-dimethylaminophenyl. As to the question of antecedent basis for this substituent, claim 20 has be modified to indicate that the aromatic ring system is substituted or unsubstituted and thus provides antecedent basis for the limitation.

With respect to paragraph 5 k) – The term "optionally selected from" has been removed from all claims where this issue could arise.

With respect to paragraph 5 l) – The claims have been modified to provide for the replacement of the term “hydrocarbon” with “alkyl” and, in addition provide further clarification of all other possible substituents.

With respect to paragraph 5 m) - Claim 46 has been modified to remove the term or phrase “are from ....” in order avoid this question.

With respect to paragraph 5 n) - Claim 48 has been modified to avoid this issue by listing appropriate halogens and removing non-halogens from the list of possibilities.

With respect to paragraph 5 o) The Examiner has determined that the claim is indefinite”in not specifying at what point and how the “compound” is “covalently” coupled to a receptor.” However, claim 49 depends indirectly on claim 20 which provides for substitution on the molecule wherein the substituents are moieties such as –COOH, -NH<sub>2</sub>, -OH and –SH, specifically identified as coupling groups by claim 33, **and** which may appear at various parts of the molecule as represented by substituents R<sub>1</sub>-R<sub>7</sub> and R<sub>9</sub>-R<sub>12</sub>. Thus, the claim does provide for the specificity as to where and how the compounds of the invention are to be coupled to other materials.

With respect to paragraph 5 p) - Claim 26 has been modified so as to more clearly define those compounds which are intended to be covered. As modified, claim 26 can be seen to encompass compounds as disclosed which may have 4 or 5 rings. Those compounds are structurally presented at pages 8-10 of the specification. Thus, compounds IVa and IVb of claim 31 find the



appropriate and necessary antecedent basis in claim 26 on which claim 31 depends.

Thus, it is believed that the issues raised under 35 USC § 112, second paragraph as to the pending claims have been removed.

Withdrawal of the rejection under 35 USC § 112, second paragraph and entry of the proposed amendments as to all pending claims is thus respectfully requested.

#### **REJECTION OF CLAIMS 20-25 AND 44-47 UNDER 35 U.S.C. §103(a)**

At page 6 the Examiner has rejected claims 20-25 and 44-47 as being unpatentable over Hallas, Aaron (X), Aaron (R), Barker or Mueller taken in combination with each of Dorval or Bandman for reasons set forth in paragraph 15 of the Office action of September 26, 2003. Paragraph 15 refers back to paragraphs 12 – 15 for discussion of the primary references.

In paragraph 12, the Examiner states:

- a) The compound of formula (III) of Hallas wherein R = adamantyl anticipates a compound of formula I of claim 26 wherein R4 is defined as "cyclic hydrocarbon" (see definitions of claim 20).
- b) Compounds (VIII) and IX of Aaron et al. (X) anticipate a compound of formula I of claim 26 wherein R3 and R4 "form a ring system containing one or more multiple bonds" (see definitions of claim 20).
- c) Compounds (V) and VI of Aaron et al. [R] wherein R = ethyl anticipate compounds of claim 26 wherein R4 = ethyl
- d) Compound (V) of Barker et al. wherein R = *p*-C<sub>6</sub>H<sub>4</sub>-NMe<sub>2</sub> anticipates a compound of formula I of claim 26 wherein R4 is substituted phenyl (see claim 20 definitions).

- e) The compound of column 6, line 35 of Mueller et al anticipates a compound of claim 26 wherein R2 and R3 "form a ring system containing one or more multiple bonds" (See the definition of claim 20).

The Examiner stated at page 8, paragraph 15, of the Office action of September 26, 2003:

Dorval et al and Bandman et al are applied for their teaching that fluorescent dyes of the type claimed herein and of the type described in references a) are useful as labels in immunoassays and nucleic acid hybridization assays. See Dorval et al, col. 6, lines 48-col. 7, line 60; col. 8, lines 49-65; in particular col. 7, line 22; Bandman et al. col. 8, line 63-col. 9, line 16, in particular col. 9, line 8.

The Examiner concludes:

It would have be obvious to substitute the fluorescent dyes of references a) as equivalent fluorescent labels in the immunoassays and nucleic hybridization assays of references b), as claimed with the expectation of obtaining similarly useful assays based on a florescence detection method.

Applicants submit that, as now amended and presented, the primary references relied upon by the Examiner either fail to disclose compounds which are carbopyronines falling within the scope of the pending claims, or the references fail to provide the teaching or evidence necessary to support a conclusion of obviousness relied on by the Examiner.

As to Hallas, applicants note that the reference does not disclose a ring system as presently claimed having the defined substituents. Specifically, the Examiner has referred to compounds of structure III wherein R is adamantyl. However, the only compounds disclosed or described wherein the R is adamantyl in the compounds of structure I and II, not the triaryl ring system of structure III. Applicants urges the Examiner to note in the first paragraph of the

article that R is defined for structure I. The absorption spectra data, which follows, provides data for structure III, only wherein R is Bu<sup>t</sup>. Noting the first complete paragraph of page 92 of Hallas will indicate that while the reference refers to structures I and II wherein R is adamantyl. No compound is ever described having the structure of III wherein R is disclosed as being adamantyl. Thus, this reference does not describe a compound within the scope of the present claims.

As to Aaron (X), the Examiner has referenced that portion of the reference in column 2, of page 321, specifically compounds (VIII) and (IX). While this reference appears to disclose compounds similar to those designated in the rejected claims, the reference provides no suggestion or description of any type of use for such compounds. The focus of the reference appears to be a study of the steric effects which result in such compounds due to particular substituents. Thus, as discussed below in considering the Mueller reference, it is applicants' position that the reference does not, even taken in combination with Dorval or Bandman, provide an adequate basis or support for the conclusion of obviousness reached by the Examiner.

As to Aaron (R), the Examiner has referenced structures (V) and (VI) at page 2655 wherein R = ethyl. However, as presently amended, compounds of this type are explicitly excluded by claim 20, and therefore the claims depending thereon. As presently claimed, if R<sub>1</sub>-R<sub>3</sub> and R<sub>5</sub>-R<sub>7</sub> are hydrogen and R<sub>8</sub>, R<sub>8a</sub> and R<sub>9</sub>-R<sub>12</sub> are methyl, then R<sub>4</sub> cannot be hydrogen, ethyl, or t-butyl. Thus, Aaron (R) does not disclose compounds within the scope of the newly amended claims.

As to Barker, the Examiner has referenced Compound (V), appearing in column 2, page 1069 wherein  $R = p\text{-C}_6\text{H}_4\text{-NMe}_2$ . However, as with Aaron (R) above, this compound is now explicitly excluded from the scope of the present claims since claim 20 provides that where  $R_1\text{-}R_3$  and  $R_5\text{-}R_7$  are hydrogen, then  $R_4$  cannot be a 4-dimethylaminophenyl group. Thus, Barker does not disclose compounds within the scope of the newly amended claims.

As to Mueller, the Examiner references the compound of column 6, line 35 wherein  $R_2$  and  $R_3$  forms a ring system containing one or more multiple bonds. While Mueller would appear to disclose compounds closely related to those of claim 20, the reference does not disclose these compounds as dyes suitable for use in assays such as immunoassays or nucleic acid hybridization assays, but as "stable fluorescent visible absorbers" (col. 5, line 51) which are useful in optical filtering elements (Abstract). There is nothing in this reference which would suggest the suitability for use of compounds disclosed therein for the presently claimed purpose.

Thus, Hallas, Aaron (R), and Barker do not disclose or describe compounds within the scope of the present pending claims. While Aaron (X) and Mueller may describe compounds similar to those present in the claimed method, they do not provide any suggestion or direction which would have led one of ordinary skill to use these compounds in the assays as presently claimed. While Dorval mentions, in a very general disclosure, the use as labels "triarylmethane dyes" (col. 7, line 22), the reference provides no examples and no disclosure which would reasonably suggest the use of any specific compounds such as the

carbopyronines of the instant claims or those compounds disclosed by either Aaron (X) or Mueller as florescent labels in assays as presently claimed. Even if the Examiner's comments implicitly suggest a level of "obvious to try" the compounds of either Aaron or Mueller for the claim use, the combined teachings do not suggest even a slight likelihood of probable of success. Further, none of the references suggest how to couple the compounds of Aaron (X) or Mueller to a biomolecule to permit the use as claimed.

Bandman offers nothing more than that which is provided by Dorval, again suggesting the use of such compounds as quinoline dyes and triarylmethane dyes (col. 9, line 8), but providing no description which would reasonably suggest the use of the filtering materials taught and described by Aaron (X) or Mueller.

In order to support a conclusion of obviousness there must be something present in the prior art which would have suggested or directed one of ordinary skill in the art to do that which is claimed. Here, there is no suggestion to be found in either the primary references or the secondary references. Thus, the evidence of record does not adequately support the conclusion that the invention of claims 20-25 and 44-48 would have been obvious in view of the references relied on by the Examiner.

For the foregoing reasons, applicants respectfully request the Examiner reconsider this basis of rejection and withdraw the rejection of claims 20-25 and 44-48 under 35 USC § 103(a).

## **CONCLUSION**

Applicants have addressed each of the issues raised by the Examiner in the Office action of June 1, 2004. Accordingly, applicants request entry of the proposed amendment and reconsideration of all rejections in light of the amendments and comments in support thereof.

In view of the above presented remarks and amendments, it is respectfully submitted that all claims on file should be considered patentable. None of the references either disclose or suggest the carbopyronine fluorescent dies as claimed here.

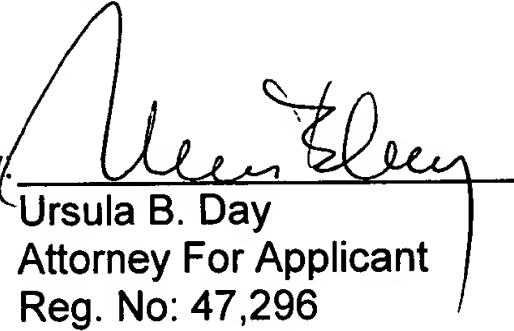
Reconsideration and allowance of the claims in the present application are respectfully requested.

Should the Examiner consider necessary or desirable any formal changes anywhere in the specification, claims and/or drawing, then it is respectfully requested that such changes be made by Examiner's Amendment, if the Examiner feels this would facilitate passage of the case to issuance. If the Examiner feels that it might be helpful in advancing this case by calling the undersigned, applicant would greatly appreciate such a telephone interview.

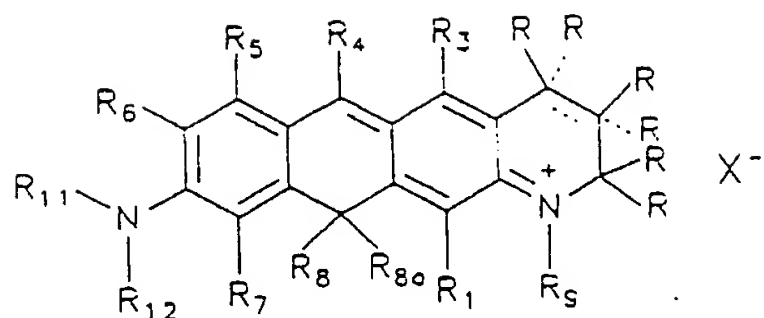
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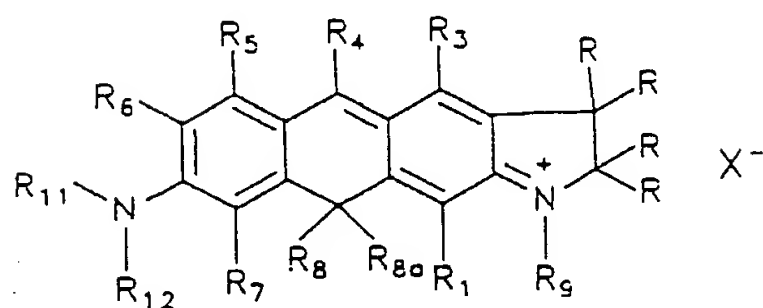
Respectfully submitted,

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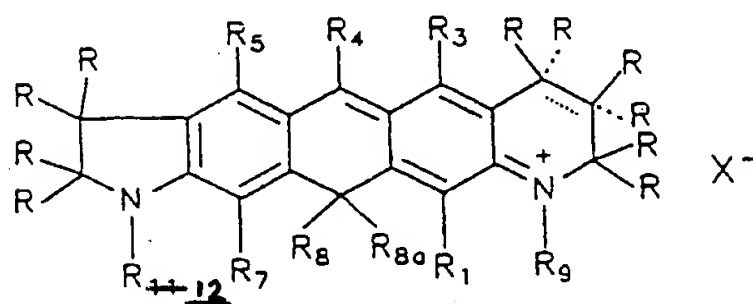
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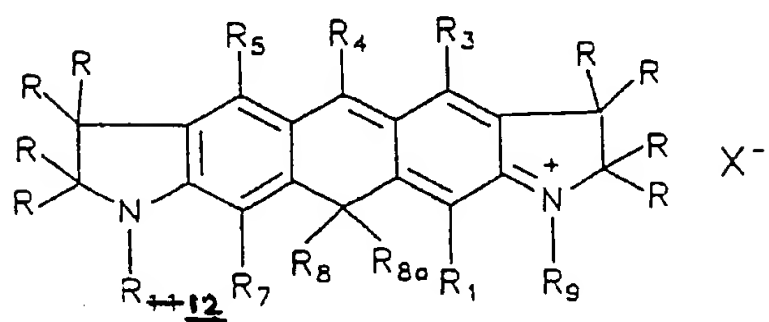
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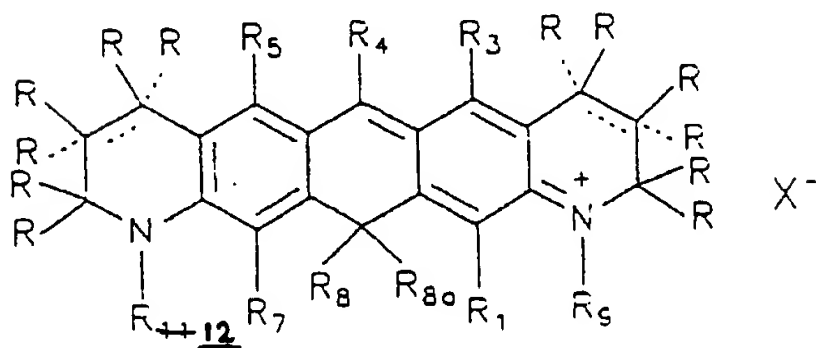
IVb



IVc



IVd



IVe